Nut and peanut butter intake are not directly associated with the risk of endometrial or ovarian cancer

Nut and peanut butter intake are not directly associated with the risk of endometrial or ovarian cancer: results from a Dutch prospective cohort study

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Abstract

Background & aims: Nut intake has been associated with reduced cancer-related mortality and cancer risk. However, very few studies investigated the association between nut consumption and the risk of endometrial and ovarian cancer, with inconclusive results. We prospectively examined the relation between total nut, tree nut, peanut, and peanut butter intake and the risk of endometrial and ovarian cancer in the prospective Netherlands Cohort Study (NLCS).

Methods: In 1986, 62,573 women aged 55-69 years were included in the NLCS. At baseline, all participants filled in a questionnaire and a subcohort of 2,589 women was randomly selected. After 20.3 years of follow-up, 389 endometrial and 347 ovarian cancer cases with complete data were included in the analysis. Hazard ratios (HRs) were calculated in multivariable-adjusted Cox regression analyses, using a case-cohort approach.

Results: Compared to nonconsumers, the HRs (95% confidence intervals) for women consuming 10+ g total nuts/day were 1.23 (0.82-1.87) for endometrial cancer and 0.84 (0.57-1.24) for ovarian cancer. For tree nut, peanut, and peanut butter intake, also no significant relations with endometrial or ovarian cancer were observed. In the endometrial cancer analyses, significant interactions of total nut intake with body mass index and cigarette smoking status were found.

Conclusions: The results of this study suggest that intake of total nuts, tree nuts, peanuts, and peanut butter is not related to the risk of endometrial or ovarian cancer. The observed interactions in the endometrial cancer analyses, in particular with cigarette smoking status, require confirmation in other studies.

Keywords: Endometrial cancer, Ovarian cancer, Nuts, Peanut butter, Cohort studies

Abbreviations: AIC, Akaike Information Criterion; aMED, alternate Mediterranean diet; BMI, body mass index; CI, confidence interval; HR, hazard ratio; NLCS, Netherlands Cohort Study; PH, proportional hazards; SD, standard deviation

Introduction

In 2012, uterine corpus cancer, which predominantly comprises endometrial cancer [1], was the fourth most common cancer in women in developed countries; ovarian cancer ranked fifth [2]. The development of endometrial cancer has mainly been linked to an excess of estrogen relative to progesterone [3]. For ovarian cancer, the most common explanation is the incessant ovulation hypothesis, which suggests that reproductive tissue turnover results in an accumulation of genetic damage [3-5]. Although endometrial and ovarian cancers are two distinct entities, these hypothesized mechanisms might apply to both cancer types [3]. Other proposed mechanisms for both cancer types relate, amongst others, to inflammation, gonadotropin stimulation, and mucin-related immunity [3, 5-7].

Recently, increased nut consumption has been associated with reduced cancer-related mortality and cancer risk [8-15]. Several animal and human studies stated that phytoestrogens in nuts (isoflavonoids and lignans) might modify sex hormone metabolism and activity, thereby possibly reducing the risk of hormone-dependent cancers [16, 17]. Other proposed mechanisms by which nuts have been suggested to conduct their cancer-chemopreventive effects relate, amongst others, to their antioxidant activity, regulation of immunological and anti-inflammatory responses, and regulation of cell proliferation and differentiation [16, 18-20].

Very few studies investigated the association between nut consumption and the risk of endometrial and ovarian cancer, with contradictive results: to our knowledge, only three case-control studies were performed for endometrial cancer [21-23], and one cohort [24] and two case-control studies for ovarian cancer [25, 26]. Because these studies are inconclusive and because prospective evidence regarding these relations is very limited, we investigated the role of tree nut, peanut, and peanut butter consumption in the development of endometrial and ovarian cancer in the prospective Netherlands Cohort Study on diet and cancer (NLCS).

Materials and methods

Study design and cancer follow-up

The NLCS was initiated in September 1986, when 62,573 women aged 55-69 years were enrolled [27]. These women agreed to participate by filling in and returning a baseline questionnaire, which measured dietary habits and other cancer risk factors. Ethical approval of the NLCS was obtained from the institutional review boards of the Maastricht University and the Netherlands Organization for Applied Scientific Research (TNO). The NLCS was conducted in accordance with the Declaration of Helsinki. A case-cohort approach was applied to improve

67 the efficiency of the data processing and analysis. Following this approach, incident cases were derived from the
68 entire cohort, whereas person-years at risk were estimated from a subcohort. This subcohort consisted of 2,589
69 women who were randomly sampled from the total cohort directly after baseline. Subcohort members were
70 followed up biennially for vital status information until December 2006. After 20.3 years of follow-up
71 (September 1986 until December 2006), no subcohort members were lost to follow-up.

72 Follow-up for cancer incidence was performed through annual record linkage with the Netherlands Cancer
73 Registry and the Netherlands Pathology Registry (PALGA) [28]. The completeness of the cancer follow-up was
74 estimated to be higher than 95% [29].

75 After 20.3 years of follow-up, 551 incident endometrial and 498 incident ovarian cancer cases were detected.
76 Prevalent cancer cases (except for skin cancer), non-epithelial or borderline invasive cases, or cases without
77 microscopic confirmation were excluded. Participants were excluded if they had a hysterectomy (excluded from
78 the endometrial cancer analysis) or an oophorectomy (excluded from the ovarian cancer analysis). Moreover,
79 cases and subcohort members with incomplete or inconsistent dietary data, or with missing data on confounders
80 were also excluded. Applying these criteria resulted in 1,452 subcohort members and 389 endometrial cancer
81 cases for the analyses of endometrial cancer, and 1,646 subcohort members and 347 ovarian cancer cases for the
82 analyses of ovarian cancer (Figure 1).

83 **Exposure assessment**

84 Smoking habits, physical activity, anthropometrics, dietary intakes, and other cancer risk factors were evaluated
85 with a mailed, self-administered, 11-page baseline questionnaire. Information about habitual diet in the year
86 preceding baseline was assessed with a validated 150-item semi-quantitative food frequency questionnaire [30].
87 Intake of peanuts, tree nuts, and peanut butter was estimated by asking for intake frequencies and number of
88 standard portion sizes consumed per intake of ‘peanuts’, ‘other, mixed nuts’ (tree nuts), and ‘peanut butter’.
89 Intake frequencies could range from ‘never or less than 1x/month’ to ‘6-7x/week’. A standard portion size was
90 assumed 28 g for tree nuts and peanuts, and 15 g per slice of bread for peanut butter. Daily intakes were
91 calculated by multiplying intake frequencies and portion sizes. Total nut intake was calculated as the sum of
92 daily tree nut and peanut intake.

93 **Statistical analysis**

The relation between nut and peanut butter intake and the risk of endometrial and ovarian cancer was analyzed in age- and multivariable-adjusted Cox regression analyses. The proportional hazards (PH) assumption was evaluated with Schoenfeld residuals [31], log-log survival plots, and by including time-varying covariates. No violations of this assumption were observed in the endometrial and ovarian cancer analyses for the exposure variables. In case the PH assumption was violated for confounders, time-covariate interactions for those variables were included. Standard errors were calculated with the robust Huber-White sandwich estimator to account for the additional variance introduced by the sampling from the entire cohort [32].

The relation between nut and peanut butter intake and endometrial and ovarian cancer risk was tested on a categorical and continuous scale (per 5 g/day increment). For the categorical analyses, total nut and peanut intake were divided into categories of 0, 0.1-<5, 5-<10, and 10+ g/day, and tree nut and peanut butter intake into 0, 0.1-<5, and 5+ g/day, because of the lower number of cases in the higher intake categories. Linear trends were investigated by assigning median nut intake values in the subcohort to the intake categories and fitting these as a continuous variable in the regression models.

In the multivariable-adjusted models, estimates were adjusted for the following predefined confounders: age (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day; continuous, centered), and duration (years; continuous, centered)), body mass index (BMI; <18.5, 18.5-<25, 25-<30, ≥30 kg/m^2), nonoccupational physical activity (≤30, >30-60, >60-90, >90 min/day), educational level (primary or lower vocational (low), secondary or medium vocational (medium), higher vocational or university (high)), age at menarche (years; continuous), age at menopause (years; continuous), parity and age at first child birth (nulliparous, 1-2 children - <25 years, 1-2 children - ≥25 years, ≥3 children - <25 years, ≥3 children - ≥25 years), oral contraceptive use (never, ever), hormone replacement therapy use (never, ever), daily energy intake (kcal/day; continuous), and the alternate Mediterranean diet (aMED) score excluding alcohol and nuts [33] (0-2, 3-4, 5-7 points). In the endometrial cancer analyses, we additionally adjusted for family history of endometrial cancer (no, yes), and in the ovarian cancer analyses for family history of breast cancer (no, yes). Initially, we also adjusted the ovarian cancer analyses for family history of ovarian cancer. However, because only three participants reported a positive family history, this factor was excluded from the final model, which did not importantly change the estimates. We also checked the following potential confounders: intake of coffee, nutritional supplement use, history of diabetes (for the endometrial cancer analyses only), history of hypertension (for the endometrial cancer analyses only), hysterectomy (for the ovarian cancer analyses only),

and height. Because these variables did not change the estimates with minimally 10% when using a backward stepwise selection procedure, they were excluded from the final model.

To further investigate the linearity of the exposure-response relation between nut and peanut butter intake and endometrial and ovarian cancer risk, we performed restricted cubic splines analyses with three fixed knots at 0, 5, and 10 g intake/day. To examine the assumptions regarding the number and placement of knots, we compared the fit of several models with additional knots or different knot positions using the Akaike Information Criterion (AIC) score [34].

Potential residual confounding and interactions were investigated by stratifying the relation between total nut intake and endometrial and ovarian cancer by BMI, nonoccupational physical activity, cigarette smoking status, educational level, and aMED score excluding alcohol and nuts. For ovarian cancer, we also investigated potential interactions by family history of breast cancer (no, yes). We could not stratify by family history of endometrial cancer (in the endometrial cancer analysis) or by family history of ovarian cancer (in the ovarian cancer analysis), because of the limited number of participants with a positive family history. The total nut intake categories of 5-<10 g/day and 10+ g/day were merged to increase statistical power. Participant with a BMI <18.5 kg/m^2 were excluded from the analysis stratified by BMI because of the small number of cases in this category. Interactions were tested by including cross-product terms in the Cox models and performing Wald tests.

To check for potential reversed causation, we excluded the first two years of follow-up. Secondly, we divided the total follow-up duration in two-year periods and compared the median baseline nut and peanut butter intake of cases diagnosed during these periods, using a Kruskal-Wallis test. Moreover, we restricted the analysis of peanut butter to participants who had stated having had a constant peanut butter intake in the five years preceding baseline. These data were not available for tree nut or peanut intake. In another sensitivity analyses, we adjusted for consumption of fruits, vegetables, dairy and cheese, and red and processed meat instead of the aMED score excluding alcohol and nuts. Furthermore, associations of tree nut, peanut, and peanut butter intake with endometrial and ovarian cancer were mutually adjusted.

Analyses were performed with Stata 15 software (StataCorp. 2017. College Station, TX). P-values were tested two-sided and were considered statistically significant if <0.05.

Results

In the analyses of endometrial cancer, mean (SD) total nut intake was slightly higher in cases (4.4 (8.6) g/day) than in the subcohort (4.2 (7.8) g/day) (Table 1). In the ovarian cancer analyses, mean (SD) total nut intake was 4.2 (8.4) g/day among cases and 4.4 (8.6) g/day among subcohort members. Average intakes of tree nuts, peanuts, and peanut butter were almost similar in subcohort members and endometrial and ovarian cancer cases.

Regarding other baseline characteristics, both endometrial and ovarian cancer cases were on average less physically active and less often ever cigarette smokers, parous, or oral contraceptive users than subcohort members. Moreover, endometrial and ovarian cancer cases had a later mean age at menopause and scored lower on the aMED score excluding alcohol and nuts (Table 1). Furthermore, compared to subcohort members, endometrial cancer cases were on average heavier, lower educated, reported a positive family history of endometrial cancer more often, had a lower age at menarche, and used hormone replacement therapy more often. Ovarian cancer cases more often reported a positive family history of ovarian cancer than subcohort members, but less often a positive family history of breast cancer, and they used hormone replacement therapy less often.

Age- and multivariable-adjusted associations between nut and peanut butter intake and endometrial and ovarian cancer risk are presented in Table 2. In the age-adjusted analyses, no statistically significant relation of total nut intake was found with endometrial or ovarian cancer risk (HR (95% CI) for 10+ g/day vs. nonconsumers = 1.03 (0.71-1.49), p-trend = 0.743, and 0.83 (0.57-1.20), p-trend = 0.305, respectively). Tree nut, peanut, and peanut butter consumption were also not significantly related to endometrial or ovarian cancer risk in age-adjusted analyses. After multivariable-adjustment, the nonsignificant positive associations between total nut and peanut intake and endometrial cancer risk became somewhat stronger, whereas the nonsignificant inverse associations between tree nut and peanut butter intake and endometrial cancer risk attenuated or became positive. For ovarian cancer, multivariable-adjustment did not change the results importantly. Total nut intake was not significantly associated with endometrial or ovarian cancer risk after multivariable-adjustment (HR (95% CI) for 10+ g/day vs. nonconsumers = 1.23 (0.82-1.87), p-trend = 0.449, and 0.84 (0.57-1.24), p-trend = 0.452, respectively). Also no significant relations with endometrial or ovarian cancer were observed for tree nut, peanut, and peanut butter intake. In continuous analyses, nut and peanut butter consumption were also not related to the risk of endometrial or ovarian cancer.

In restricted cubic spline analyses with three fixed knots at 0, 5, and 10 g nut intake/day, no statistical evidence for nonlinear relations with endometrial or ovarian cancer risk were observed for all four exposure variables (Figure 2). However, the tests for nonlinearity were borderline significant for the relations between peanut butter

intake and endometrial cancer risk (p-nonlinearity = 0.062) and between total nut intake and ovarian cancer risk (p-nonlinearity = 0.081). When using additional knots or different knot positions, the model fit, as measured with the AIC score, did not improve importantly (data not shown).

Table 3 and Supplementary Table 1 present the associations between total nut intake and endometrial and ovarian cancer risk in strata of potential effect modifiers. In the analyses of endometrial cancer stratified by BMI, no significant association between total nut intake and endometrial cancer risk was observed in participants with a BMI of 18.5-<25 kg/m^2 (Table 3). A nonsignificant positive trend was observed in participants with a BMI ≥25 kg/m^2, with a significantly increased risk in the category of 0.1-<5 g total nut intake/day compared to nonconsumers (HR (95% CI) = 1.68 (1.13-2.48)). The test for interaction by BMI was significant (p-interaction = 0.016). For cigarette smoking status, no relation between total nut intake and endometrial cancer risk was found in never smokers, a nonsignificant positive association in former smokers, and a significant positive trend in current smokers (HR (95% CI) for 5+ g/day vs nonconsumers = 3.49 (1.25-9.73), p-trend = 0.021). The p-interaction by smoking status was 0.019. In Figure 3, we further investigated the joint effects of total nut intake and cigarette smoking status on endometrial cancer risk, with never smokers who consumed 0 g total nuts/day as reference category. Increasing nut intake attenuated the inverse association between former cigarette smoking and endometrial cancer risk, and in women who consumed 5+ g total nuts/day, current smoking was even associated with a non-significantly increased endometrial cancer risk. In never smokers, no significant relation between nut intake and endometrial cancer was observed. Nevertheless, only currently smoking nonconsumers had a significantly lower endometrial cancer risk than never smoking nonconsumers (HR (95% CI) = 0.45 (0.25-0.81)). For ovarian cancer, no significant interactions between total nut intake and potential effect modifiers were observed (Supplementary Table 1).

No significant differences were found in the median baseline nut and peanut butter intake of endometrial and ovarian cancer cases diagnosed over the follow-up period in Kruskal-Wallis tests (p ≥0.206) (data not shown). Exclusion of the first two years of follow-up resulted in similar results as when the total follow-up period was included (data not shown). Moreover, restricting the analyses of the relation between peanut butter intake and endometrial and ovarian cancer risk to those participants who had stated having had a constant peanut butter intake in the five years before baseline also did not importantly change the results (data not shown).

In another sensitivity analysis, adjustment for intake of fruits, vegetables, dairy and cheese, and red and processed meat gave similar estimates as when adjusting for the aMED score excluding nuts and alcohol (data

not shown). Moreover, mutually adjusting intake of tree nuts, peanuts, and peanut butter in relation to endometrial and ovarian cancer risk also did not change the results (data not shown).

Discussion

In the current study, total nut intake was not significantly related to the risk of endometrial or ovarian cancer. Similar results were found for tree nut, peanut, and peanut butter intake. For the relation between total nuts and endometrial cancer risk, we observed significant interactions by BMI and cigarette smoking status.

Our results for ovarian cancer are in line with the results from the Swedish Women's Lifestyle and Health Cohort Study [24], in which also no statistically significant association between nut consumption and ovarian cancer risk was observed. To our knowledge, this is the only other prospective cohort study investigating the relation between nut intake and ovarian cancer risk. No other prospective evidence is available for endometrial cancer.

Besides the abovementioned cohort study, only two case-control studies have been performed on this topic for ovarian cancer [25, 26], and three case-control studies for endometrial cancer [21-23]. Regarding ovarian cancer, a Canadian case-control study did not find a relation between nut product intake frequency and ovarian cancer risk [26], and in an Australian case-control study, intake of omega-6 fatty acids from nuts was significantly associated with a reduced risk of epithelial ovarian cancer [25]. Because the relation of omega-6 fatty acids with ovarian cancer risk varied between the food sources of the omega-6 fatty acids, the authors stated that the estimates probably reflect a relation with nuts rather than with omega-6 fatty acids [25].

Regarding endometrial cancer, one case-control study in Greece observed significant positive associations for intake of pulses and nuts combined [23], whereas a later Greek case-control study found a significant inverse association for pulse, nut, and seed consumption together [21]. In a Japanese case-control study, consuming peanuts ≥1-2x/week was associated with a significantly reduced risk of endometrial endometrioid carcinoma [22]. A borderline significant inverse trend was seen when peanut intake was expressed as intake density (g/1000 kcal) [22]. Case-control studies are prone to selection and information biases, which may explain the contradictive results for both endometrial and ovarian cancer. Furthermore, none of the above-mentioned studies investigated the interaction between nut intake and cigarette smoking. Thus, the evidence on the relation between nut intake and endometrial and ovarian cancer is very limited, and further (prospective) research is required to confirm our results.

For endometrial cancer, we observed significant interactions of total nut intake with BMI. However, only the category of 0.1-<5 g total nut intake/day was significantly associated with an increased endometrial cancer risk in participants with a BMI higher than 25 kg/m^2, and no significant exposure-response trends were observed in both BMI strata. Because of the number of significance tests performed, this finding may be due to chance. Nuts are energy-dense foods, and therefore concerns have been raised about weight gain resulting from increased nut intake. In case of hormone-dependent cancers, like endometrial and ovarian cancer, this is especially important because of the hormonal activity of adipose tissue [3, 35, 36]. However, several cross-sectional and prospective studies have indicated that higher nut intake is actually associated with reduced weight gain and a lower risk of becoming overweight or obese [37-40].

The interaction between total nut intake and cigarette smoking in relation to endometrial cancer risk was also significant. In contrast to most cancer sites, cigarette smoking has been associated with a lower risk of endometrial cancer, particularly among postmenopausal women [41, 42]. This protective effect is hypothesized to be related to a reduction in the level of circulating unopposed estrogens: smoking has been found to modify the production and metabolism of estrogens, androgens, and progesterone, and to reduce body weight [41-43]. Moreover, smoking might have direct cytotoxic effects on the ovaries, which causes oocyte destruction and induces earlier menopause [42, 43]. In our study, increasing total nut intake appeared to counteract the protective effect of smoking (Figure 3), and even a non-significantly increased endometrial cancer risk was found in current smokers who consumed at least 5 g nuts/day. One possible explanation for this observation is that phytoestrogens in nuts might have estrogenic activity if the circulating concentration of unopposed endogenous estrogens is low [17, 44], which possibly counteracts the protective antiestrogenic effects of smoking. Nuts also contain several components with antioxidant, anti-inflammatory, and cell metabolism-modifying properties [16, 19], which might also potentially oppose the effects of smoking. However, this is the first study investigating the interaction between nut intake and cigarette smoking in relation to endometrial cancer risk, and this finding needs to be confirmed in other studies first.

Our study has some limitations. Only baseline measurements were performed, while dietary intakes may have changed over the 20.3 year follow-up period. Nevertheless, dietary habits appeared to be quite stable for at least five years in a reproducibility study [45]. Potential measurement error might have resulted in misclassification and thus in an attenuation of the results. Moreover, potential residual confounding by measured and unmeasured confounders cannot be excluded. For example, we had no information on risk factors like breastfeeding and tubal

ligation. Because these factors are unlikely to be associated with nut intake, they are not expected to confound our results.

Strengths of the study are the prospective nature and the long and complete follow-up, which make selection and information bias unlikely. The large number of participants allowed us to extensively correct for potential confounders. Moreover, we were able to distinguish between tree nut, peanut, and peanut butter intake.

In conclusion, the results of this prospective cohort study suggest that total nut, tree nut, peanut, and peanut butter intake are not related to the risk of endometrial or ovarian cancer. The observed interactions of nut intake in relation to endometrial cancer risk, in particular with cigarette smoking, need confirmation in other studies.

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References

[1] Lortet-Tieulent J, Ferlay J, Bray F, Jemal A. International Patterns and Trends in Endometrial Cancer Incidence, 1978-2013. J Natl Cancer Inst. 2018;110:354-61.

[2] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359-86.

[3] Cramer DW. The epidemiology of endometrial and ovarian cancer. Hematol Oncol Clin North Am. 2012;26:1-12.

[4] Fathalla MF. Incessant ovulation--a factor in ovarian neoplasia? Lancet. 1971;2:163.

[5] Hunn J, Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. Clin Obstet Gynecol. 2012;55:3-23.

[6] Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst. 1999;91:1459-67.

[7] Terry KL, Titus-Ernstoff L, McKolanis JR, Welch WR, Finn OJ, Cramer DW. Incessant ovulation, mucin 1 immunity, and risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:30-5.

[8] Bao Y, Han J, Hu FB, Giovannucci EL, Stampfer MJ, Willett WC, et al. Association of nut consumption with total and cause-specific mortality. N Engl J Med. 2013;369:2001-11.

[9] Bonaccio M, Di Castelnuovo A, De Curtis A, Costanzo S, Bracone F, Persichillo M, et al. Nut consumption is inversely associated with both cancer and total mortality in a Mediterranean population: prospective results from the Moli-sani study. Br J Nutr. 2015;114:804-11.

[10] Gopinath B, Flood VM, Burlutksy G, Mitchell P. Consumption of nuts and risk of total and cause-specific mortality over 15 years. Nutr Metab Cardiovasc Dis. 2015;25:1125-31.

[11] Guasch-Ferre M, Bullo M, Martinez-Gonzalez MA, Ros E, Corella D, Estruch R, et al. Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. BMC Med. 2013;11:164.

[12] Luu HN, Blot WJ, Xiang YB, Cai H, Hargreaves MK, Li H, et al. Prospective evaluation of the association of nut/peanut consumption with total and cause-specific mortality. JAMA Intern Med. 2015;175:755-66.

[13] van den Brandt PA, Schouten LJ. Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: a cohort study and meta-analysis. Int J Epidemiol. 2015;44:1038-49.

[14] Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. BMC Med. 2016;14:207.

312 [15] Wu L, Wang Z, Zhu J, Murad AL, Prokop LJ, Murad MH. Nut consumption and risk of cancer and type 2
313 diabetes: a systematic review and meta-analysis. Nutr Rev. 2015;73:409-25.
314 [16] Gonzalez CA, Salas-Salvado J. The potential of nuts in the prevention of cancer. Br J Nutr. 2006;96 Suppl
315 2:S87-94.
316 [17] Adlercreutz H. Phytoestrogens: epidemiology and a possible role in cancer protection. Environ Health
317 Perspect. 1995;103 Suppl 7:103-12.
318 [18] Casari I, Falasca M. Diet and Pancreatic Cancer Prevention. Cancers (Basel). 2015;7:2309-17.
319 [19] Falasca M, Casari I, Maffucci T. Cancer chemoprevention with nuts. J Natl Cancer Inst. 2014;106.
320 [20] Ros E. Health benefits of nut consumption. Nutrients. 2010;2:652-82.
321 [21] Petridou E, Kedikoglou S, Koukoulomatis P, Dessypris N, Trichopoulos D. Diet in relation to endometrial
322 cancer risk: a case-control study in Greece. Nutr Cancer. 2002;44:16-22.
323 [22] Takayama S, Monma Y, Tsubota-Utsugi M, Nagase S, Tsubono Y, Numata T, et al. Food intake and the
324 risk of endometrial endometrioid adenocarcinoma in Japanese women. Nutr Cancer. 2013;65:954-60.
325 [23] Tzonou A, Lipworth L, Kalandidi A, Trichopoulou A, Gamatsi I, Hsieh CC, et al. Dietary factors and the
326 risk of endometrial cancer: a case--control study in Greece. Br J Cancer. 1996;73:1284-90.
327 [24] Hedelin M, Lof M, Andersson TM, Adlercreutz H, Weiderpass E. Dietary phytoestrogens and the risk of
328 ovarian cancer in the women's lifestyle and health cohort study. Cancer Epidemiol Biomarkers Prev.
329 2011;20:308-17.
330 [25] Ibiebele TI, Nagle CM, Bain CJ, Webb PM. Intake of omega-3 and omega-6 fatty acids and risk of ovarian
331 cancer. Cancer Causes Control. 2012;23:1775-83.
332 [26] Pan SY, Ugnat AM, Mao Y, Wen SW, Johnson KC, Canadian Cancer Registries Epidemiology Research G.
333 A case-control study of diet and the risk of ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2004;13:1521-7.
334 [27] van den Brandt PA, Goldbohm RA, van 't Veer P, Volovics A, Hermus RJ, Sturmans F. A large-scale
335 prospective cohort study on diet and cancer in The Netherlands. J Clin Epidemiol. 1990;43:285-95.
336 [28] Van den Brandt PA, Schouten LJ, Goldbohm RA, Dorant E, Hunen PM. Development of a record linkage
337 protocol for use in the Dutch Cancer Registry for Epidemiological Research. Int J Epidemiol. 1990;19:553-8.
338 [29] Goldbohm RA, van den Brandt PA, Dorant E. Estimation of the coverage of Dutch municipalities by cancer
339 registries and PALGA based on hospital discharge data. Tijdschr Soc Gezondheidsz. 1994;72:80-4.

[30] Goldbohm RA, van den Brandt PA, Brants HA, van't Veer P, Al M, Sturmans F, et al. Validation of a dietary questionnaire used in a large-scale prospective cohort study on diet and cancer. Eur J Clin Nutr. 1994;48:253-65.

[31] Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika. 1982;69:239-41.

[32] Lin DY, Wei LJ. The Robust Inference for the Cox Proportional Hazards Model. Journal of the American Statistical Association. 1989;84:1074-8.

[33] van den Brandt PA, Schulpen M. Mediterranean diet adherence and risk of postmenopausal breast cancer: results of a cohort study and meta-analysis. Int J Cancer. 2017.

[34] Akaike H. A new look at the statistical model identification. IEEE Trans Automat Control. 1974;AC-19:716-23.

[35] Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, et al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol. 2013;31:2607-18.

[36] Webb PM. Obesity and gynecologic cancer etiology and survival. Am Soc Clin Oncol Educ Book. 2013.

[37] Freisling H, Noh H, Slimani N, Chajes V, May AM, Peeters PH, et al. Nut intake and 5-year changes in body weight and obesity risk in adults: results from the EPIC-PANACEA study. Eur J Nutr. 2017.

[38] Bes-Rastrollo M, Sabate J, Gomez-Gracia E, Alonso A, Martinez JA, Martinez-Gonzalez MA. Nut consumption and weight gain in a Mediterranean cohort: The SUN study. Obesity (Silver Spring). 2007;15:107-16.

[39] Bes-Rastrollo M, Wedick NM, Martinez-Gonzalez MA, Li TY, Sampson L, Hu FB. Prospective study of nut consumption, long-term weight change, and obesity risk in women. Am J Clin Nutr. 2009;89:1913-9.

[40] Jackson CL, Hu FB. Long-term associations of nut consumption with body weight and obesity. Am J Clin Nutr. 2014;100 Suppl 1:408S-11S.

[41] Terry PD, Rohan TE, Franceschi S, Weiderpass E. Cigarette smoking and the risk of endometrial cancer. Lancet Oncol. 2002;3:470-80.

[42] Zhou B, Yang L, Sun Q, Cong R, Gu H, Tang N, et al. Cigarette smoking and the risk of endometrial cancer: a meta-analysis. Am J Med. 2008;121:501-8 e3.

[43] Viswanathan AN, Feskanich D, De Vivo I, Hunter DJ, Barbieri RL, Rosner B, et al. Smoking and the risk of endometrial cancer: results from the Nurses' Health Study. Int J Cancer. 2005;114:996-1001.

[44] Rietjens I, Louisse J, Beekmann K. The potential health effects of dietary phytoestrogens. Br J Pharmacol. 2017;174:1263-80.

370 [45] Goldbohm RA, van 't Veer P, van den Brandt PA, van 't Hof MA, Brants HA, Sturmans F, et al.
371 Reproducibility of a food frequency questionnaire and stability of dietary habits determined from five annually
372 repeated measurements. Eur J Clin Nutr. 1995;49:420-9.

373

374 **Table 1.** Baseline characteristics (mean (SD) or %) of subcohort members and endometrial and ovarian cancer

375 cases in the Netherlands Cohort Study, 1986-2006

	Endometrial cancer		**Ovarian cancer**	
	Subcohort[a]	Cases	Subcohort[a]	Cases
N	1,452	389	1,646	347
Age (years)	61.4 (4.2)	61.4 (4.3)	61.3 (4.2)	61.5 (4.2)
Never cigarette smoker (%)	58.9	66.8	58.4	64.6
Body Mass Index (kg/m^2)	25.0 (3.5)	26.4 (4.1)	25.0 (3.5)	25.1 (3.6)
Non-occupational physical activity (min/day)	66.3 (51.0)	58.6 (46.3)	66.0 (50.4)	57.8 (37.5)
University or higher vocational education (%)	9.7	8.7	9.7	9.5
Family history of endometrial cancer (%)	2.8	4.4		
Family history of ovarian cancer (%)			0.1	0.6
Family history of breast cancer (%)			8.7	7.8
Age at menarche (years)	13.7 (1.8)	13.4 (1.6)	13.7 (1.8)	13.7 (1.8)
Age at menopause (years)	49.1 (4.3)	50.2 (3.9)	48.9 (4.4)	49.3 (3.9)
Parous (%)	81.2	73.5	81.8	76.1
Age at first birth (in parous, years)	27.1 (4.2)	27.1 (3.9)	27.0 (4.2)	27.6 (4.1)
Number of children (in parous, n)	3.4 (1.9)	3.1 (1.7)	3.4 (1.9)	3.2 (1.7)
Ever used oral contraceptives (%)	24.5	13.9	25.3	19.0
Ever used hormone replacement therapy (%)	11.8	16.5	13.4	12.4
Daily energy intake (kcal)	1,687 (390)	1,658 (398)	1,688 (392)	1,695 (389)
Total nut intake (g/day)	4.2 (7.8)	4.4 (8.6)	4.4 (8.6)	4.2 (8.4)
Tree nut intake (g/day)	1.0 (2.7)	1.0 (3.0)	1.1 (4.1)	1.0 (2.9)
Peanut intake (g/day)	3.3 (6.8)	3.4 (6.9)	3.3 (6.9)	3.2 (6.6)
Peanut butter intake (g/day)	1.2 (3.6)	1.1 (3.2)	1.2 (3.5)	1.2 (3.7)
aMED score (excl. alcohol and nuts) of 5-7 pts (%)	26.5	23.1	26.6	23.9

376 [a] The subcohort sizes of the endometrial and ovarian cancer analyses differ because of differences in the in- and

377 exclusion criteria (Figure 1).

378 **Table 2.** Age- and multivariable-adjusted HRs (and 95% CIs) for endometrial and ovarian cancer according to nut consumption; NLCS, 1986-2006

	Endometrial cancer					Ovarian cancer				
	Median intake[a]	Person-years	Cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR[b] (95% CI)	Median intake[a]	Person-years	Cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR[b] (95% CI)
Total nuts (g/day)										
0	0.0	9,912	143	1.00 (reference)	1.00 (reference)	0.0	11,388	158	1.00 (reference)	1.00 (reference)
0.1-<5	2.1	9,500	160	1.18 (0.91-1.53)	1.26 (0.94-1.67)	2.1	10,817	117	0.80 (0.61-1.04)	0.79 (0.59-1.05)
5-<10	7.8	2,876	37	0.91 (0.60-1.38)	1.21 (0.76-1.92)	7.8	3,115	28	0.68 (0.43-1.06)	0.71 (0.45-1.14)
10+	15.5	3,338	49	1.03 (0.71-1.49)	1.23 (0.82-1.87)	15.7	3,919	44	0.83 (0.57-1.20)	0.84 (0.57-1.24)
P_{trend}				0.743	0.449				0.305	0.425
Continuous, per 5 g/day increment				1.01 (0.93-1.08)	1.06 (0.97-1.14)				0.98 (0.91-1.06)	0.99 (0.91-1.07)
Tree nuts (g/day)										
0	0.0	17,973	277	1.00 (reference)	1.00 (reference)	0.0	20,505	248	1.00 (reference)	1.00 (reference)
0.1-<5	1.6	6,204	93	0.98 (0.75-1.27)	1.03 (0.76-1.39)	1.6	7,008	85	1.02 (0.78-1.33)	1.04 (0.77-1.41)
5+	8.9	1,450	19	0.85 (0.51-1.43)	1.08 (0.62-1.90)	8.9	1,727	14	0.69 (0.38-1.23)	0.71 (0.39-1.32)
P_{trend}				0.543	0.767				0.226	0.317

Continuous, per 5 g/day increment				0.99 (0.78-1.25)	1.06 (0.83-1.36)				0.94 (0.80-1.12)	0.96 (0.82-1.13)
Peanuts (g/day)										
0	0.0	11,772	175	1.00 (reference)	1.00 (reference)	0.0	13,535	182	1.00 (reference)	1.00 (reference)
0.1-<5	2.1	9,548	151	1.08 (0.84-1.39)	1.20 (0.91-1.57)	2.0	10,791	111	0.78 (0.60-1.02)	0.81 (0.61-1.06)
5-<10	8.5	2,063	31	1.03 (0.66-1.61)	1.19 (0.73-1.96)	8.5	2,249	21	0.73 (0.44-1.19)	0.75 (0.45-1.26)
10+	14.4	2,242	32	0.97 (0.63-1.49)	1.16 (0.73-1.85)	17.1	2,666	33	0.94 (0.63-1.43)	0.96 (0.62-1.47)
P_{trend}				0.896	0.499				0.699	0.792
Continuous, per 5 g/day increment				1.01 (0.93-1.09)	1.06 (0.98-1.16)				0.99 (0.90-1.08)	1.00 (0.91-1.10)
Peanut butter (g/day)										
0	0.0	18,388	298	1.00 (reference)	1.00 (reference)	0.0	21,173	257	1.00 (reference)	1.00 (reference)
0.1-<5	1.2	4,654	58	0.77 (0.57-1.06)	0.83 (0.59-1.17)	1.2	5,275	55	0.87 (0.63-1.20)	0.88 (0.63-1.21)
5+	5.3	2,584	33	0.79 (0.53-1.18)	0.84 (0.54-1.30)	5.3	2,792	35	1.05 (0.71-1.56)	1.02 (0.67-1.54)
P_{trend}				0.186	0.359				0.896	0.989
Continuous, per 5 g/day increment				0.92 (0.77-1.11)	0.96 (0.79-1.17)				1.02 (0.85-1.22)	1.00 (0.83-1.21)

379 [a] Median intake in the female subcohort.

[b] Adjusted for age (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day; continuous, centered), and duration (years; continuous, centered)), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2), nonoccupational physical activity (≤30, >30-60, >60-90, >90 min/day), educational level (low, medium, high), family history of endometrial cancer (no, yes; in the endometrial cancer analysis only), family history of breast cancer (no, yes; in the ovarian cancer analysis only), age at menarche (years; continuous), age at menopause (years; continuous), parity and age at first child birth (nulliparous, 1-2 children - <25 years, 1-2 children - ≥25 years, ≥3 children - <25 years, ≥3 children - ≥25 years), oral contraceptive use (never, ever), hormone replacement therapy use (never, ever), daily energy intake (kcal/day; continuous), alternate Mediterranean diet score excluding alcohol and nuts (0-2, 3-4, 5-7 points).

386 **Table 3.** Multivariable-adjusted associations between total nut intake and endometrial cancer risk in strata of

387 potential effect modifiers; NLCS, 1986-2006

	Total nut consumption (g/day)			P_{trend}	$P_{interaction}$
	0 g/day	0.1-<5 g/day	5+ g/day		
Endometrial cancer					
Overall					
Cases/person-time at risk (years)	143/9,912	160/9,500	86/6,214		
HR (95% CI)[a]	1.00 (reference)	1.26 (0.94-1.67)	1.22 (0.86-1.74)	0.410	
Body mass index[b]					
18.5-<25 kg/m^2					
Cases/person-time at risk (years)	65/4,959	51/5,085	48/4,121		
HR (95% CI)[a]	1.00 (reference)	0.76 (0.49-1.18)	1.07 (0.65-1.77)	0.512	0.016
25+ kg/m^2					
Cases/person-time at risk (years)	76/4,768	108/4,343	38/2,033		
HR (95% CI)[a]	1.00 (reference)	1.68 (1.13-2.48)	1.24 (0.73-2.09)	0.775	
Nonoccupational physical activity					
≤30 min/day					
Cases/person-time at risk (years)	46/2,650	44/1,752	23/1,073		
HR (95% CI)[a]	1.00 (reference)	1.44 (0.83-2.50)	1.24 (0.56-2.73)	0.689	0.650
>30-≤60 min/day					
Cases/person-time at risk (years)	36/3,029	56/3,121	33/2,109		
HR (95% CI)[a]	1.00 (reference)	1.74 (1.01-3.00)	1.61 (0.83-3.12)	0.341	
>60-≤90 min/day					
Cases/person-time at risk (years)	31/2,153	32/2,392	13/1,447		
HR (95% CI)[a]	1.00 (reference)	0.93 (0.45-1.91)	0.84 (0.36-1.94)	0.682	
>90 min/day					
Cases/person-time at risk (years)	30/2,080	28/2,235	17/1,585		
HR (95% CI)[a]	1.00 (reference)	0.97 (0.40-2.33)	0.96 (0.36-2.54)	0.937	
Cigarette smoking status					
Never					

	Cases/person-time at risk (years)	106/6,166	114/5,791	40/3,320		
	HR (95% CI)[a]	1.00 (reference)	1.21 (0.86-1.71)	0.83 (0.51-1.35)	0.322	0.019
Former						
	Cases/person-time at risk (years)	20/1,507	28/2,148	24/1,758		
	HR (95% CI)[a]	1.00 (reference)	1.23 (0.55-2.78)	1.32 (0.56-3.07)	0.594	
Current						
	Cases/person-time at risk (years)	17/2,239	18/1,562	22/1,137		
	HR (95% CI)[a]	1.00 (reference)	1.97 (0.78-4.94)	3.49 (1.25-9.73)	0.021	
Educational level						
Low						
	Cases/person-time at risk (years)	84/6,013	92/4,941	37/2,673		
	HR (95% CI)[a]	1.00 (reference)	1.50 (1.02-2.21)	1.32 (0.79-2.21)	0.397	0.620
Medium						
	Cases/person-time at risk (years)	49/3,316	54/3,507	39/2,696		
	HR (95% CI)[a]	1.00 (reference)	1.05 (0.62-1.77)	1.11 (0.59-2.09)	0.752	
High						
	Cases/person-time at risk (years)	10/583	14/1,052	10/845		
	HR (95% CI)[a]	1.00 (reference)	0.84 (0.14-5.16)	0.64 (0.10-4.05)	0.576	
Adapted Mediterranean diet score excluding nuts and alcohol						
0-2 points						
	Cases/person-time at risk (years)	35/2,980	50/2,088	17/1,372		
	HR (95% CI)[a]	1.00 (reference)	2.22 (1.15-4.28)	1.27 (0.54-2.99)	0.883	0.169
3-4 points						
	Cases/person-time at risk (years)	79/4,855	74/4,596	44/2,875		
	HR (95% CI)[a]	1.00 (reference)	1.04 (0.69-1.57)	1.23 (0.74-2.05)	0.424	
5-7 points						
	Cases/person-time at risk (years)	29/2,077	36/2,817	25/1,967		
	HR (95% CI)[a]	1.00 (reference)	0.87 (0.43-1.74)	1.05 (0.48-2.28)	0.720	

388 [a] Adjusted for age (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day;
389 continuous, centered), and duration (years; continuous, centered)), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2),
390 nonoccupational physical activity (≤30, >30-60, >60-90, >90 min/day), educational level (low, medium, high),

family history of endometrial cancer (no, yes), age at menarche (years; continuous), age at menopause (years; continuous), parity and age at first child birth (nulliparous, 1-2 children - <25 years, 1-2 children - ≥25 years, ≥3 children - <25 years, ≥3 children - ≥25 years), oral contraceptive use (never, ever), hormone replacement therapy use (never, ever), daily energy intake (kcal/day; continuous), alternate Mediterranean diet score excluding alcohol and nuts (0-2, 3-4, 5-7 points).

[b] Participants with a BMI <18.5 kg/m^2 (n = 22) were excluded from the interaction analysis.

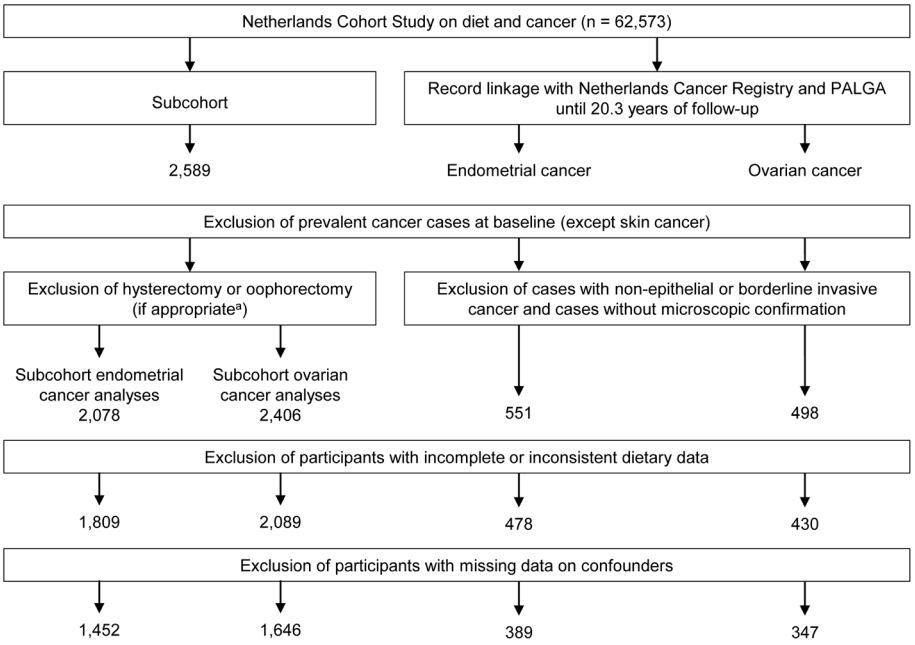
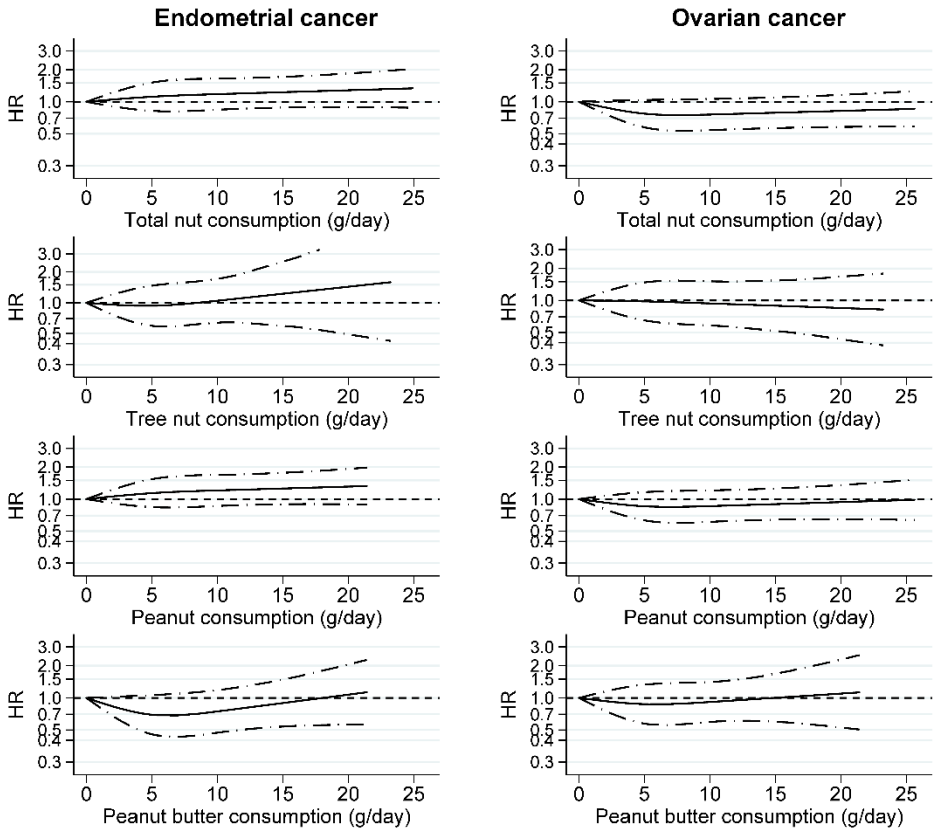


Figure 1. Flow chart of the number of subcohort members and ovarian and endometrial cancer cases; the NLCS, 1986-2006

[a] Hysterectomy excluded from the analysis of endometrial cancer, oophorectomy excluded from the analysis of ovarian cancer



412 **Figure 2.** Restricted cubic spline analyses with three fixed knots at 0, 5, and 10 g intake/day, investigating the
413 relation between nut and peanut butter consumption and the risk of endometrial and ovarian cancer. Solid lines
414 represent HRs, dashed lines 95% confidence limits. P-values for nonlinearity for total nut, tree nut, peanut, and
415 peanut butter intake were 0.724, 0.558, 0.640, and 0.062 for endometrial cancer, and 0.081, 0.911, 0.283, and
416 0.492 for ovarian cancer, respectively. Results were adjusted for age (years; continuous), cigarette smoking
417 (status (never, former, current), frequency (n/day; continuous, centered), and duration (years; continuous,
418 centered)), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2), nonoccupational physical activity (≤30, >30-60, >60-90,
419 >90 min/day), educational level (low, medium, high), family history of endometrial cancer (no, yes; in the
420 endometrial cancer analyses only), family history of breast cancer (no, yes; in the ovarian cancer analyses only),
421 age at menarche (years; continuous), age at menopause (years; continuous), parity and age at first child birth
422 (nulliparous, 1-2 children - <25 years, 1-2 children - ≥25 years, ≥3 children - <25 years, ≥3 children - ≥25 years),
423 oral contraceptive use (never, ever), hormone replacement therapy use (never, ever), daily energy intake
424 (kcal/day; continuous), alternate Mediterranean diet score excluding alcohol and nuts (0-2, 3-4, 5-7 points)

425

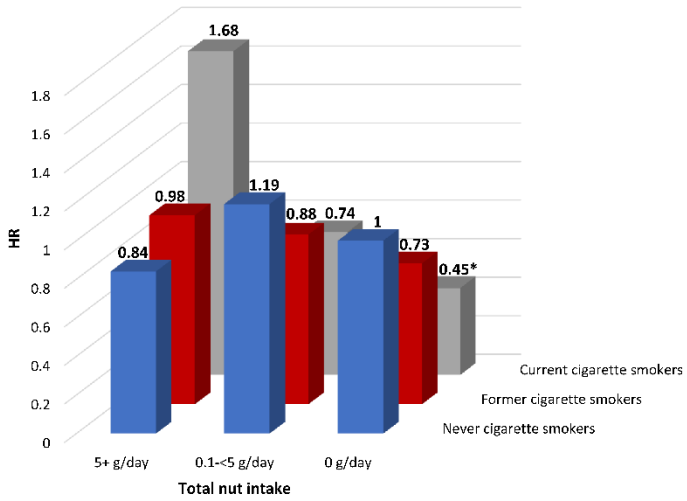


Figure 3. Combined exposure to total nuts and cigarette smoking and the risk of endometrial cancer; the NLCS, 1986-2006. Never cigarette smokers who consumed 0 g nuts/day are the reference category. Results were adjusted for age (years; continuous), cigarette smoking (frequency (n/day; continuous, centered) and duration (years; continuous, centered)), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2); nonoccupational physical activity (≤30, >30-60, >60-90, >90 min/day), educational level (low, medium, high), family history of endometrial cancer (no, yes), age at menarche (years; continuous), age at menopause (years; continuous), parity and age at first child birth (nulliparous, 1-2 children - <25 years, 1-2 children - ≥25 years, ≥3 children - <25 years, ≥3 children - ≥25 years), oral contraceptive use (never, ever), hormone replacement therapy use (never, ever), daily energy intake (kcal/day; continuous), alternate Mediterranean diet score excluding alcohol and nuts (0-2, 3-4, 5-7 points)

* indicates a significant association ($p<0.05$)

Supplementary Table 1. Multivariable-adjusted associations between total nut intake and ovarian cancer risk in strata of potential effect modifiers; NLCS, 1986-2006

	Total nut consumption (g/day)			P_{trend}	$P_{interaction}$
	0 g/day	0.1-<5 g/day	5+ g/day		
Ovarian cancer					
Overall					
Cases/person-time at risk (years)	158/11,388	117/10,817	72/7,034		
HR (95% CI)[a]	1.00 (reference)	0.79 (0.60-1.05)	0.78 (0.56-1.10)	0.258	
Body mass index[b]					
18.5-<25 kg/m^2					
Cases/person-time at risk (years)	78/5,765	65/5,651	38/4,666		
HR (95% CI)[a]	1.00 (reference)	0.96 (0.65-1.42)	0.71 (0.45-1.13)	0.135	0.194
25+ kg/m^2					
Cases/person-time at risk (years)	80/5,389	51/5,095	32/2,309		
HR (95% CI)[a]	1.00 (reference)	0.61 (0.39-0.95)	0.85 (0.50-1.46)	0.869	
Nonoccupational physical activity					
≤30 min/day					
Cases/person-time at risk (years)	44/2,942	24/2,033	17/1,287		
HR (95% CI)[a]	1.00 (reference)	0.73 (0.38-1.38)	0.77 (0.37-1.57)	0.534	0.718
>30-≤60 min/day					
Cases/person-time at risk (years)	56/3,411	46/3,580	21/2,418		
HR (95% CI)[a]	1.00 (reference)	0.77 (0.47-1.26)	0.59 (0.32-1.10)	0.125	
>60-≤90 min/day					
Cases/person-time at risk (years)	34/2,633	27/2,720	22/1,657		
HR (95% CI)[a]	1.00 (reference)	0.69 (0.36-1.32)	0.95 (0.47-1.93)	0.827	
>90 min/day					
Cases/person-time at risk (years)	24/2,403	20/2,485	12/1,672		
HR (95% CI)[a]	1.00 (reference)	0.89 (0.42-1.91)	0.85 (0.35-2.06)	0.743	
Cigarette smoking status					

Never						
	Cases/person-time at risk (years)	103/7,077	82/6,612	39/3,677		
	HR (95% CI)[a]	1.00 (reference)	0.84 (0.59-1.19)	0.73 (0.47-1.13)	0.193	0.399
Former						
	Cases/person-time at risk (years)	27/1,744	19/2,444	17/2,008		
	HR (95% CI)[a]	1.00 (reference)	0.47 (0.22-0.99)	0.48 (0.21-1.08)	0.219	
Current						
	Cases/person-time at risk (years)	28/2,567	16/1,761	16/1,349		
	HR (95% CI)[a]	1.00 (reference)	0.94 (0.44-1.99)	1.53 (0.66-3.51)	0.283	
Educational level						
Low						
	Cases/person-time at risk (years)	87/6,909	60/5,730	41/3,156		
	HR (95% CI)[a]	1.00 (reference)	0.85 (0.58-1.26)	1.08 (0.67-1.73)	0.654	0.304
Medium						
	Cases/person-time at risk (years)	60/3,780	43/3,904	23/2,933		
	HR (95% CI)[a]	1.00 (reference)	0.62 (0.38-0.99)	0.47 (0.26-0.85)	0.031	
High						
	Cases/person-time at risk (years)	11/669	14/1,183	8/946		
	HR (95% CI)[a]	1.00 (reference)	2.38 (0.39-14.46)	0.92 (0.18-4.57)	0.583	
Family history of breast cancer						
No						
	Cases/person-time at risk (years)	147/10,472	107/9,679	66/6,527		
	HR (95% CI)[a]	1.00 (reference)	0.81 (0.60-1.10)	0.79 (0.56-1.12)	0.267	0.699
Yes						
	Cases/person-time at risk (years)	11/916	10/1,138	6/507		
	HR (95% CI)[a]	1.00 (reference)	0.53 (0.13-2.18)	0.83 (0.18-3.75)	0.960	
Adapted Mediterranean diet score excluding nuts and alcohol						
0-2 points						
	Cases/person-time at risk (years)	41/3,362	37/2,430	15/1,506		

HR (95% CI)[a]	1.00 (reference)	1.36 (0.71-2.61)	0.75 (0.36-1.55)	0.299	0.165
3-4 points					
Cases/person-time at risk (years)	82/5,625	56/5,199	33/3,306		
HR (95% CI)[a]	1.00 (reference)	0.72 (0.48-1.08)	0.72 (0.44-1.18)	0.286	
5-7 points					
Cases/person-time at risk (years)	35/2,401	24/3,188	24/2,223		
HR (95% CI)[a]	1.00 (reference)	0.55 (0.29-1.04)	0.98 (0.47-2.01)	0.620	

[a] Adjusted for age (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day; continuous, centered), and duration (years; continuous, centered)), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2), nonoccupational physical activity (≤30, >30-60, >60-90, >90 min/day), educational level (low, medium, high), family history of breast cancer (no, yes), age at menarche (years; continuous), age at menopause (years; continuous), parity and age at first child birth (nulliparous, 1-2 children - <25 years, 1-2 children - ≥25 years, ≥3 children - <25 years, ≥3 children - ≥25 years), oral contraceptive use (never, ever), hormone replacement therapy use (never, ever), daily energy intake (kcal/day; continuous), alternate Mediterranean diet score excluding alcohol and nuts (0-2, 3-4, 5-7 points).

[b] Participants with a BMI <18.5 kg/m^2 (n = 25) were excluded from the interaction analysis.